

# The Alkalinizing Effects of Metabolizable Bases in the Healthy Calf

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## ABSTRACT

The alkalinizing effect of citrate, acetate, propionate, gluconate, L and DL-lactate were compared in healthy neonatal calves. The calves were infused for a 3.5 hour period with 150 mmol/L solutions of the sodium salts of the various bases. Blood pH, base excess, and metabolite concentrations were measured and the responses compared with sodium bicarbonate and sodium chloride infusion. D-gluconate and D-lactate had poor alkalinizing abilities and accumulated in blood during infusion suggesting that they are poorly metabolized by the calf. Acetate, L-lactate and propionate had alkalinizing effects similar to bicarbonate, although those of acetate had a slightly better alkalinizing effect than L-lactate. Acetate was more effectively metabolized because blood acetate concentrations were lower than L-lactate concentrations. There was a tendency for a small improvement in metabolism of acetate and lactate with age. Sodium citrate infusion produced signs of hypocalcemia, presumably because it removed ionized calcium from the circulation.

D-gluconate, D-lactate and citrate are unsuitable for use as alkalinizing agents in intravenous fluids. Propionate, acetate and L-lactate are all good alkalinizing agents in healthy calves but will not be as effective in situations where tissue metabolism is impaired.

**Key words:** Alkalinizing agent, alkalinizing effect, infusion, calves.

## RÉSUMÉ

Cette expérience visait à comparer l'effet alcalifiant du citrate, de l'acétate, du propionate, du gluconate, du L et du DL-lactate, chez des veaux sains et nouveau-nés. Les veaux reçurent à cette fin, en infusions intraveineuses d'une durée de 3,5 heures, des solutions qui contenaient 150 mmol/L des sels de sodium des bases précitées. On mesura ensuite le pH sanguin, l'excès basique et les concentrations de métabolites et on compara les résultats avec ceux de l'infusion de bicarbonate et de chlorure de sodium. Le D-gluconate et le D-lactate possédaient un piètre pouvoir alcalifiant et s'accumulèrent dans le sang, au cours de leur infusion, indice que leur métabolisation est très limitée, chez le veau. L'acétate, le L-lactate et le propionate possédaient des effets alcalifiants semblables à ceux du bicarbonate; ceux de l'acétate étaient cependant légèrement supérieurs à ceux du L-lactate. L'acétate afficha une métabolisation plus efficace que le L-lactate, parce qu'il s'accumula moins dans le sang. La métabolisation de l'acétate et du lactate sembla s'améliorer, avec l'âge. L'infusion de citrate de sodium produisit des signes d'hypocalcémie, probablement parce qu'il élimina du sang le calcium ionisé.

Le D-gluconate, le D-lactate et le citrate sont inutilisables comme agents alcalifiants dans des solutions destinées à l'infusion intraveineuse. Le propionate, l'acétate et le L-lactate représentent autant de bons agents alcalifiants, chez les veaux en santé; ils ne seront toutefois pas aussi efficaces,

en présence d'une altération du métabolisme tissulaire.

**Mots clés:** agent alcalifiant, effet alcalifiant, infusion, veaux.

## INTRODUCTION

Diarrheic calves which are presented to veterinarians for treatment often have a severe acidosis which cannot be readily corrected simply by infusing fluids (1). Bicarbonate has been shown to be highly effective in correcting metabolic acidosis in diarrheic calves (1). However, metabolizable bases — such as lactate, acetate or gluconate — are often used rather than bicarbonate because they are more easily sterilized and are thought to be slower acting and are thus less likely to produce paradoxical cerebrospinal fluid acidosis and cellular hypoxia (2,3). A disadvantage of metabolizable bases is the dependence on the body's metabolism.

Studies comparing the alkalinizing efficacy of metabolizable bases administered intravenously to calves are difficult to find. The objectives of this study were to compare the alkalinizing response of a variety of bases to determine which produced an alkalinizing effect in the healthy calf. It was thought that some bases would not be metabolized by the calf, particularly very young calves, and thus would not be suitable for use as alkalinizing agents. Others might be metabolized but be associated with side effects that made them unsuitable for use in intravenous fluids.

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## MATERIALS AND METHODS

### ANIMALS

Seventeen Holstein male calves were bought from local farmers. The calves were kept in individual pens in rooms maintained at between 10 and 25°C. All calves in a given experiment received the same diet of either whole cows milk or commercial milk replacer. The calves were fed twice daily. Hay and calf starter was offered free choice from 14 days of age. In experiment 1 five calves were used. They were  $9.6 \pm 8.8$  (mean  $\pm$  1 standard deviation) and  $17.2 \pm 7.8$  days old at the beginning and end of the experiment respectively. They weighed  $47.4 \pm 10.5$  kg at the beginning of the experiment. Six calves were used in experiment 2. They were  $5.2 \pm 5.4$  and  $14.3 \pm 4.5$  days old at the beginning and end of the experiment respectively, they weighed  $44.8 \pm 7.4$  kg at the beginning of the experiment. In experiment 3 six calves were given one set of infusions when they were between two and five days of age, the infusions were then repeated between 11 and 18 days of age. The calves weighed  $41.6 \pm 8.4$  kg during the first series of infusions and  $44.8 \pm 6.3$  kg during the second series. Experiment 4 used the calves which had just completed experiment 2; they were  $17.7 \pm 2.7$  days old at the end of this trial.

### EXPERIMENTAL DESIGN

The alkalinizing response of various bases in healthy calves was compared in two experiments. In experiment 1 the alkalinizing effects of the sodium salts of L-lactate, acetate and D-gluconate were compared with bicarbonate and chloride. In experiment 2 the alkalinizing effects of the sodium salts of L-lactate, DL-lactate, propionate, and bicarbonate were compared. The DL-lactate used in this experiment was an approximately equal mixture of D and L-lactate; the infusions contained 80.1 and 75.0 mmol/L of D and L-lactate respectively by assay. In experiment 3 the effect of age on the metabolism of lactate and acetate was studied. The calves were infused with sodium L-lactate and acetate between two and five days of age and again when the

calves were over ten days of age. In experiment 4 the tolerance of calves to intravenous trisodium citrate infusion was investigated. They were infused until signs of weakness were observed. Each calf received two citrate infusions, one autoclaved and one not. Experiment 5 was performed *in vitro*. Aqueous solutions of calcium chloride and calcium citrate containing 0, 1, 2 and 3 mmol/L of calcium ion were made up and the available calcium assayed. Serum was then collected from five calves and citric acid was added to four aliquots from each calf to produce final concentrations of 0, 1, 2 and 4 mmol/L of added citrate. The available calcium was then assayed.

### INFUSIONS

Experiments 1 to 4 involved infusion of various substances into calves. All calves were infused with isotonic solutions (150 mmol/L) of the base dissolved in distilled water. In a given experiment each calf was infused with all the bases. The order of infusions was randomized, there were at least 18 hours between each infusion.

The solutions were made by adding the powdered salt to sterile water. Citrate infusions were carried out using two types of infusion, in one type trisodium citrate powder was added to sterile water and then infused; in the other the solution was autoclaved at 124°C for 35 minutes prior to infusion. Infusions were started between one and two hours after the morning feed and continued for 3.5 hours. The infusion rate was 12.66 mL/min; either a continuous automatic infusion/withdrawal pump (model 600-950, Harvard Apparatus Company, Dover, Massachusetts) or a peristaltic pump (Masterflex pump, model 7520-00, Cole Parmer Instrument Company, Chicago, Illinois) was used for infusion.

### SAMPLING

During infusion experiments blood samples were collected from a teflon 14 gauge 64 mm jugular catheter (Surflo, Terumo Corporation, Tokyo, Japan) every half hour from zero (start of infusion) to 3.5 hours. At least 10 mL of blood and saline was discarded before collecting the samples. Blood was collected anaerobically into a heparinized 3 mL syringe

for blood gas analysis. Heparinized blood was used for packed cell volume determination. Samples for L-lactate determination were collected into a solution of sodium fluoride, citric acid, cetrимide, sodium azide and phosphate buffer (4). Blood for the assay of other bases was preserved by adding 3 mL of blood to an equal volume of ice cold L molar perchloric acid. The mixture was then centrifuged for five minutes, filtered and the filtrate neutralized with 0.5 mL of 2-molar potassium hydroxide. Serum was used for calcium and phosphorous determinations. Following each sampling the catheter was flushed with a solution of 0.9% saline containing ten units of heparin/mL. The calf's rectal temperature was also taken at each sampling time.

### LABORATORY DETERMINATIONS

Packed cell volume determinations were performed after centrifuging blood in a microhematocrit centrifuge (Damon/IEC Spinnetta Centrifuge, Needham Heights, Massachusetts) for five minutes. Blood gas determinations were performed using an automated blood gas analyzer (Corning 178 pH/blood gas analyzer, Corning Medical, Medfield, Massachusetts). The results were corrected for the calf's temperature and hemoglobin concentration (assumed to be one third of the packed cell volume). L-lactate was measured in an automated cytochrome b<sub>5</sub> dependent assay (5). D-lactate was measured using a D-lactate dehydrogenase catalyzed assay (Methods of Enzymatic Food Analysis, Boehringer Mannheim GmbH, Biochemica, Mannheim 31, W.-Germany). The assay for acetate depended on the conversion of acetate to acetyl-CoA catalyzed by acetyl-CoA synthetase followed by combination with oxaloacetate to yield citrate (Methods of Enzymatic Food Analysis, Boehringer Mannheim GmbH, Biochemica, Mannheim 31, W.-Germany). Gluconate was assayed by a gluconate kinase dependent assay (Methods of Enzymatic Food Analysis, Boehringer Mannheim GmbH, Biochemica, Mannheim 31, W.-Germany). Three standards were run with each batch of assays. The assays were verified in recovery experiments in which five different concentrations

of L-lactate, D-lactate, acetate, D-gluconate, or citrate were added to bovine blood. Calculated concentrations were compared to the amount of substance added using linear regression techniques. In all assays the correlation between the actual and assayed concentration was 0.99 or better; recoveries varied from 83 to 104%.

Serum calcium was measured by an o-cresolphthalein complex one method (Calcium procedure no. 586, Sigma Diagnostics, P.O. Box 14508, St. Louis, Missouri 63178). Phosphate was assayed using an ammonium molybdate technique (Inorganic Phosphorous Procedure No. 360-UV, Sigma Diagnostics).

#### STATISTICAL METHODS

The apparent volume of distribution ( $V_d$ ) of bicarbonate was calculated from the following equation.

$V_d = \text{mmol bicarbonate infused} \div (\text{body weight, kg} \times \text{change in base excess, mmol/L})$

Blood gas data were analyzed using analysis of variance (ANOVA) with type of base infused and calf identity as the treatment factors. In experi-

ment 3 age was added as an additional treatment factor. Initially the zero hour values were tested alone to see if there were any differences between treatment groups at the start of the experiment. A multivariate analysis of variance was then performed using a repeated measures model. Once the data had been fitted to the model treatment\*sampling time interactions were analyzed. If the interactions were not significant the main treatment effects were tested. The significance of an effect over all time periods was investigated using the Wilks' Lambda and Hotelling Lawley Trace F multivariate statistics; these two tests gave similar results. If significant base-dependent effects existed and there were more than two bases separate analyses of variance were then conducted for each time period and the means compared using Tukey's least significant difference method.

The blood concentrations of the bases were analyzed in similar fashion using multivariate analysis of variance. In experiments where both saline and bicarbonate infusions were performed a three way analysis of variance with calf identity, type of

base infused and time of sampling as the main effects was used to test whether base concentrations varied with sampling time during the infusion of saline or bicarbonate. The change in metabolite concentration from zero hour values were then compared between infusion treatments using a repeated measures multivariate analysis of variance.

Data for citrate infusions were compared using the paired t test (6). The effect of adding citrate to serum was analyzed using two way analysis of variance with added citrate concentration and calf (from which the serum was collected) as the two factors.

Linear regression calculations followed standard techniques (7).

Analysis of variance calculations were performed using SYSTAT (8) and a microcomputer (Health/Zenith HS-161, Health Co., Benton Harbor, Michigan). The data base was typed out and checked against the original work sheets to ensure the data were accurate.

Results were said to be significantly different if  $p < 0.05$  and to be nonsignificant if  $p > 0.2$ . Intermediate p values are reported.

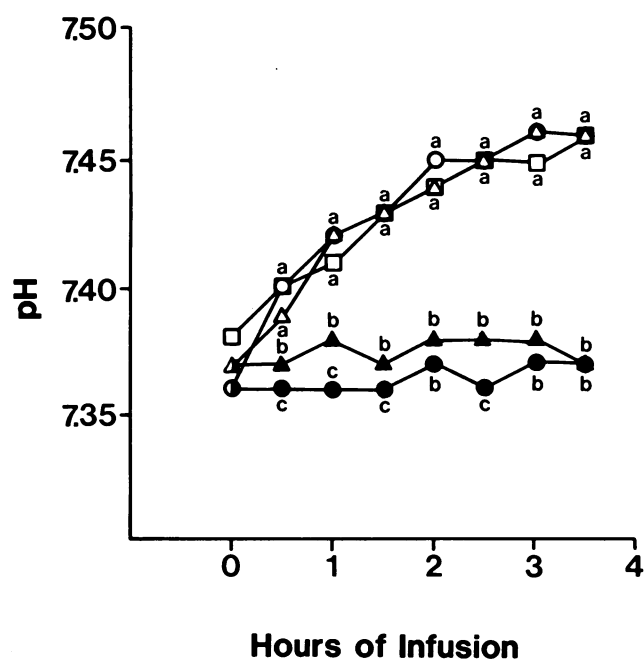


Fig. 1. The effect of continuous infusions of bicarbonate  $\Delta$ , L-lactate  $\square$ , acetate  $\circ$ , gluconate  $\bullet$  and saline  $\blacktriangle$ , on blood pH in calves. Each point is the mean of five observations, at a given time period means with different letters are significantly different at  $P < 0.05$ .

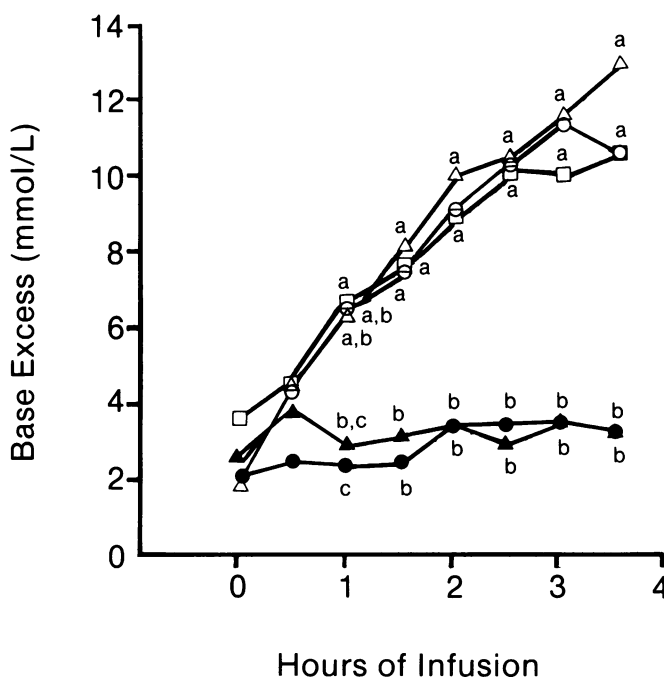


Fig. 2. The effect of continuous infusions of bicarbonate  $\Delta$ , L-lactate  $\square$ , acetate  $\circ$ , gluconate  $\bullet$  and saline  $\blacktriangle$ , on blood base excess in calves. Each point is the mean of five observations, at a given time period means with different letters are significantly different at  $P < 0.05$ .

## RESULTS

Experiment 1 compared the alkalinizing actions of L-lactate, acetate and D-gluconate. There were no differences between infusates in zero hour base excess or pH values. When the data for all time periods was analyzed there were significant time\*treatment interaction effects in both the pH and base excess data. There were significant changes in pH between most time periods, base excess values changed most between zero and one hours and between 2 and 2.5 hours of infusion. Gluconate and saline infusion produced little change in base excess or pH with time. L-lactate, acetate and bicarbonate had significant alkalinizing effects (Figs. 1 and 2). The apparent volume of distribution of bicarbonate during the bicarbonate infusion experiment was 0.73 L/kg.

The zero hour  $p\text{CO}_2$  was  $47.1 \pm 8.1$  torr. There was a marginally significant base\*time interaction effect on partial pressures of carbon dioxide in blood (Wilks' Lambda  $p = 0.111$ , Hotelling Lawley Trace  $p = 0.057$ ). None of the analyses for individual time periods showed significant differences in  $p\text{CO}_2$  between bases.

The blood concentrations of L-lactate, acetate, and gluconate during infusion of bicarbonate did not significantly differ from those found during infusion of saline. There was no tendency for the concentrations of these metabolites to change with time during bicarbonate or saline infusion. There were no significant differences in the zero hour blood lactate concentrations between the saline, bicarbonate or lactate infusion experiments; similar results were obtained when the acetate and gluconate data were analyzed. The zero hour values were  $0.91 \pm 0.44$  mmol/L for lactate,  $0.24 \pm 0.27$  for acetate and  $0.04 \pm 0.04$  for gluconate. The change in concentrations of lactate, acetate or gluconate during infusion of the respective base were plotted (Fig. 3). Over all time periods there were significant differences in the blood concentrations of the respective bases. The largest rise in blood concentration of the infused base was seen during gluconate infusions, acetate infusions produced the smallest rise and lactate produced an intermediate result.

Experiment 2 compared the metabolism of propionate, L- and DL-lactate. There were no significant differences between bases in zero hour blood base excess or pH values. Over all time periods there were significant differences in both blood pH and base excess values between infusions. DL-lactate was not as effective an alkalinizing agent as L-lactate. Propionate, L-lactate and bicarbonate were all equivalent (Figs. 4 and 5). The apparent volume of distribution for bicarbonate was 0.78.

There were significant differences between treatments in zero hour blood lactate concentrations. At the start of the bicarbonate and DL-lactate infusions zero hour D-lactate concentrations were  $0.241 \pm 0.236$  and  $0.021 \pm 0.209$  mmol/L respectively. Zero hour L-lactate concentrations were  $0.789 \pm 0.789$ ,  $0.960 \pm 0.509$  and  $0.790 \pm 0.250$  mmol/L at the start of bicarbonate, DL-lactate and L-lactate infusions respectively. The change in D or L-lactate concentration during infusion of the various bases was significantly affected by the type of base infused in a time dependent manner. During infusion of DL-lactate the change in blood D-

lactate concentration was much greater than the rise in L-lactate concentration, the D-lactate rise was also greater than that seen in L-lactate during L-lactate infusion (Fig. 6).

Experiment 3 investigated the effect of age on L-lactate and acetate metabolism. The zero hour pH values were  $7.419 \pm 0.019$  and  $7.394 \pm 0.027$  for L-lactate and acetate infusions in two to five day old calves and these were significantly higher than the values of  $7.406 \pm 0.036$  and  $7.334 \pm 0.027$  respectively for infusions at 11 to 18 days. The zero hour base excess values were  $9.9 \pm 4.1$  and  $7.2 \pm 2.8$  mmol/L for L-lactate and acetate infusions in two to five day old calves and  $9.4 \pm 4.3$  and  $2.5 \pm 4.4$  mmol/L respectively for infusions in 11 to 18 day old calves. The effect of age on zero hour base excess values was of intermediate significance,  $p = 0.12$ . The zero hour lactate and acetate concentrations were  $0.99 \pm 0.23$  and  $0.17 \pm 0.08$  in two to five day old calves and  $0.69 \pm 0.10$  and  $0.14 \pm 0.04$  respectively in 11 to 18 day old calves. The effect of age on the metabolism of L-lactate and acetate was studied after first calculating the changes in pH, base excess and

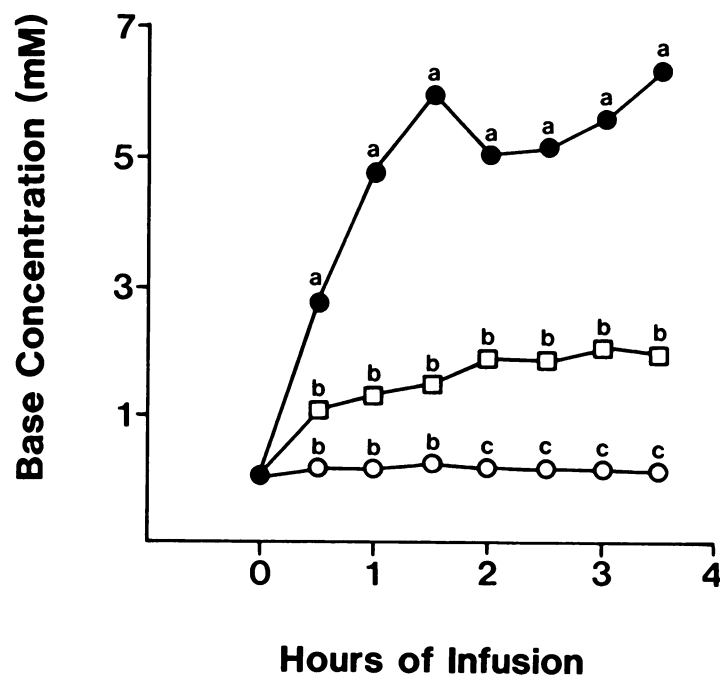


Fig. 3. The effect of continuous infusions of L-lactate  $\square$ , acetate  $\circ$  and gluconate  $\bullet$ , on the blood concentration of the infused base. Each point is the mean of five observations, at a given time period means with different letters are significantly different at  $P < 0.05$ .

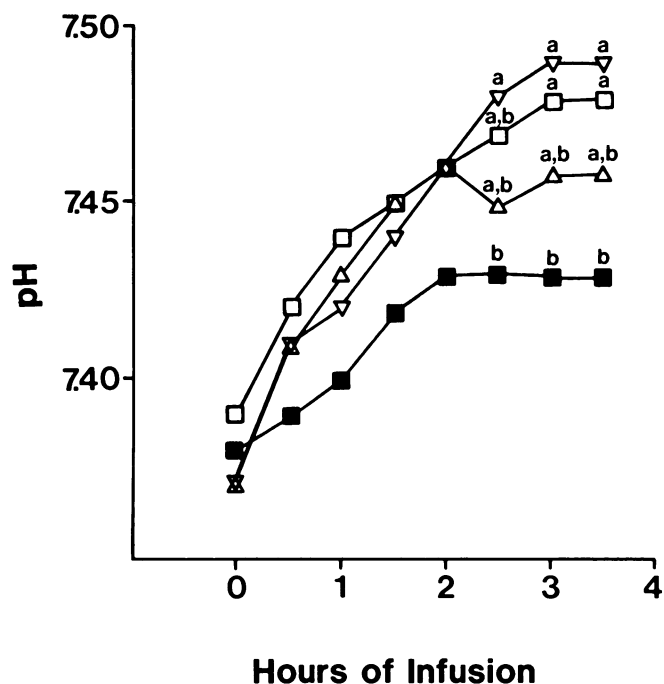


Fig. 4. The effect of continuous infusions of bicarbonate  $\triangle$ , L-lactate  $\square$ , DL-lactate  $\blacksquare$  and propionate  $\nabla$ , on blood pH in calves. Each point is the mean of five observations, at a given time period means with different letters are significantly different at  $P < 0.05$ .

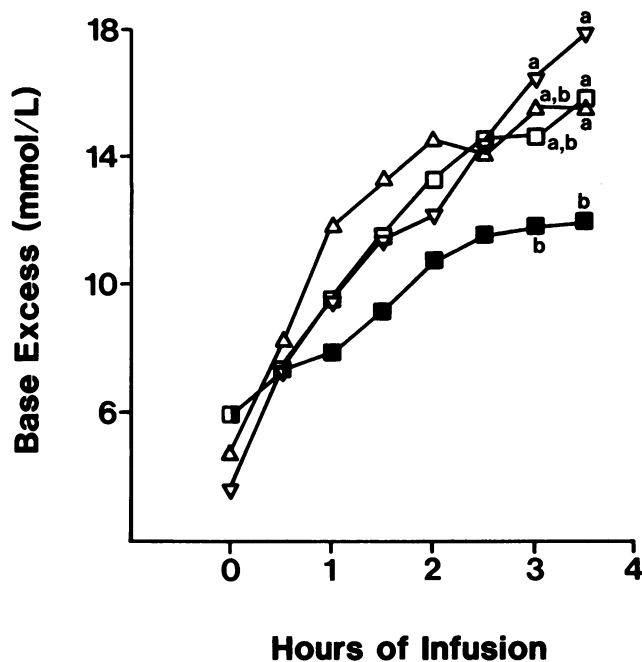


Fig. 5. The effect of continuous infusions of bicarbonate  $\triangle$ , L-lactate  $\square$ , DL-lactate  $\blacksquare$  and propionate  $\nabla$ , on blood base excess in calves. Each point is the mean of five observations, at a given time period means with different letters are significantly different at  $P < 0.05$ .

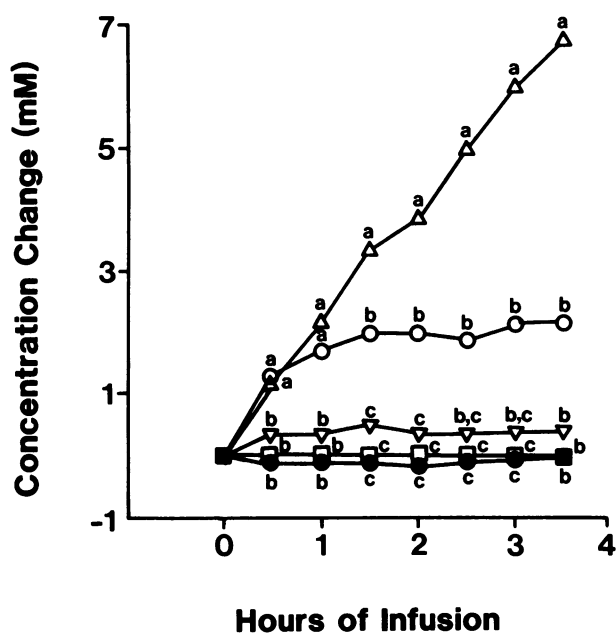


Fig. 6. The effect of continuous infusions of bicarbonate, L-lactate and DL-lactate on the change in blood concentrations of D and L-lactate. L-lactate concentrations during bicarbonate infusions are represented by  $\square$ , during L-lactate infusions by  $\circ$  and during DL-lactate infusions by  $\nabla$ . D-lactate concentrations during DL-lactate infusions are represented by  $\triangle$  and during bicarbonate infusions by  $\bullet$ . Each point is the mean change in concentration from time zero for six calves, at a given time period means with different letters are significantly different at  $P < 0.05$ .

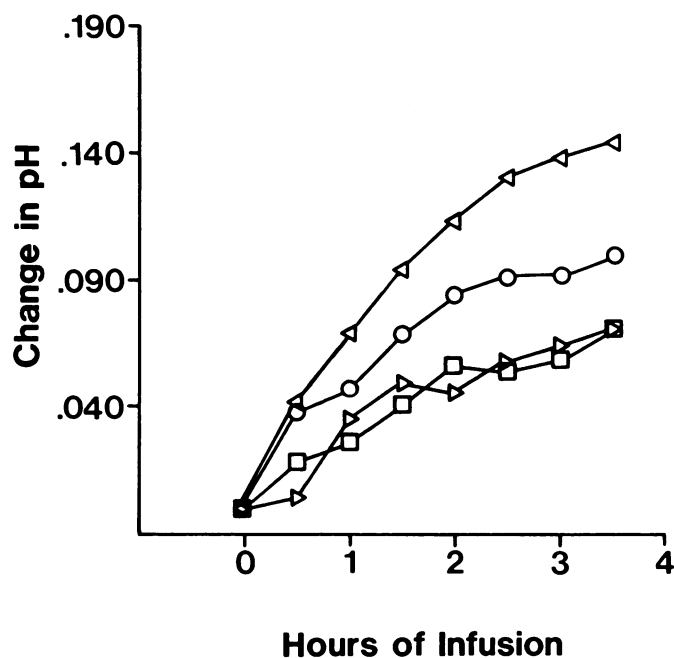


Fig. 7. Change in blood pH produced by continuous infusions of L-lactate and acetate in five calves at two to five and 11 to 18 days of age. L-lactate infusions in calves at two to five days are represented by  $\square$ , L-lactate infusions at 11 to 18 days by  $\nabla$ , acetate infusions at two to five days by  $\circ$ , acetate infusions at 11 to 18 days by  $\triangle$ . Each point represents the mean change in blood pH from zero hour values. Acetate had a significantly better alkalinizing effect than lactate and older calves showed significantly more alkalinization than younger calves.

metabolite concentration from the zero hour values. This removed variation due to changes in baseline status with age.

The alkalinizing effect of the bases improved as the calves got older. There were significant age\*sampling time interactions for blood pH. The blood base excess also tended to be affected by the calf's age,  $p = 0.054$ . Acetate had a better alkalinizing effect than L-lactate; there were significant type of infusion\*sampling time effects in the pH data and significant infusion effects in the base excess data. None of the infusion\*age interactions were significant (Figs. 7 and 8). The rises in L-lactate concentrations were significantly higher than the rises in acetate concentrations, but age did not significantly effect the change in blood metabolite concentration from zero hour values (Fig. 9).

Experiment 4 investigated the effects of citrate infusion. Calves infused with sodium citrate behaved abnormally. The first signs observed were increased licking and chewing

movements. The calves then became unsteady on their feet and positioned their feet abnormally. Recumbency followed with a transient period of stiffness of the limbs followed by flaccidity. The signs were similar in experiments with both autoclaved and nonautoclaved infusions. The infusions were stopped when the calves became unable to stand, this occurred after  $42 \pm 19$  minutes with the non-autoclaved and  $36 \pm 17$  minutes with the autoclaved solutions, this difference was not statistically significant. There were no significant differences in blood pH or base excess between the beginning and end of the infusion. Blood citrate concentrations rose significantly during infusion from  $0.07 \pm 0.04$  to  $2.30 \pm 1.19$  mmol/L. Serum calcium concentrations rose significantly from  $2.16 \pm 0.26$  to  $2.69 \pm 0.17$  mmol/L. The rise in serum phosphorous from  $2.44 \pm 0.52$  to  $2.64 \pm 0.67$  mmol/L was of doubtful significance,  $p = 0.14$ .

Experiment 5 was performed *in vitro* and investigated the effect of

citrate on the assay for calcium. The assayed concentrations of calcium in aqueous calcium chloride solutions containing 0, 1, 2 and 3 mmol/L of calcium ion were 0, 1.28, 2.32 and 3.7 mmol/L respectively. In contrast solutions of calcium citrate containing identical amounts of calcium contained 0, 0.07, 0.26 and 0.41 mmol/L respectively of calcium by assay. When citric acid was added to serum samples at the rates of 0, 1, 2 or 4 mmol/L there was no significant affect on assayed calcium concentrations of  $2.14 \pm 0.07$ ,  $2.11 \pm 0.01$ ,  $2.06 \pm 0.07$  and  $2.10 \pm 0.06$  mmol/L respectively.

## DISCUSSION

Sodium bicarbonate has an immediate alkalinizing effect because it combines directly with hydrogen ions. This reaction is catalyzed by carbonic anhydrase:

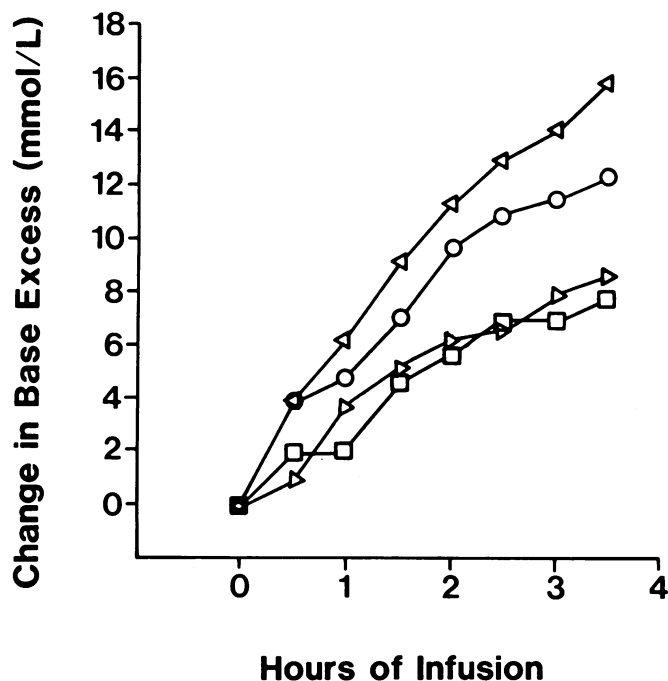


Fig. 8. Change in blood base excess produced by continuous infusions of L-lactate and acetate in five calves at two to five and 11 to 18 days of age. L-lactate infusions in calves two to five days old are represented by  $\square$ , L-lactate infusions at 11 to 18 days by  $\circ$ , acetate infusions at two to five days by  $\triangle$ , acetate infusions at 11 to 18 days by  $\diamond$ . Each point represents the mean change in blood base excess from zero hour values. Acetate had a significantly better alkalinizing effect than lactate and older calves showed significantly more alkalinization than younger calves.

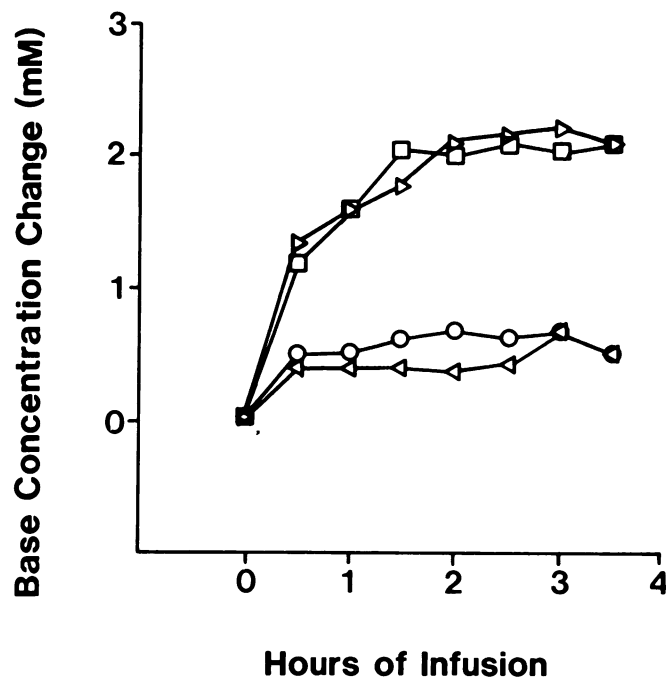
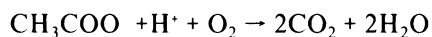
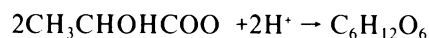
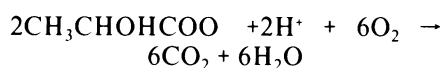


Fig. 9. Changes in blood concentrations of L-lactate and acetate during L-lactate and acetate infusion. L-lactate concentrations during L-lactate infusions in calves two to five days old are represented by  $\square$  and at 11 to 18 days by  $\circ$ . Acetate concentrations during acetate infusions at two to five days are represented by  $\triangle$  and at 11 to 18 days by  $\diamond$ . Each point represents the mean change in concentration of the infused base from zero hour values. L-lactate concentrations were significantly higher than acetate concentrations.

Tissue metabolism is required before other alkalinizing agents used in fluid therapy can exert their action. Bases such as acetate are converted to carbon dioxide and water by oxidative metabolism within mitochondria. This process requires hydrogen ions:



Lactate and propionate can either be oxidized or converted to glucose. Both processes remove hydrogen ions from the body:



The present studies shed light on the rate of tissue metabolism and alkalinizing action of various bases in the calf.

Experiments 1 and 2 indicate that the healthy neonatal calf can metabolize L-lactate, acetate and propionate very rapidly. These bases produced similar alkalinizing effects to bicarbonate. It has been suggested that the metabolism of bases would be slow and a gradual alkalinizing effect would be observed (2). However, our study indicates that metabolism is rapid and the alkalinizing effect has a similar time course to that seen with bicarbonate (Figs. 1, 2, 4 and 5). Studies in dogs also indicate that lactate, acetate and bicarbonate have similar alkalinizing effects (9). Taken together these studies do not justify the view that metabolizable bases produce a gradual alkalinizing effect.

Clinicians usually use volumes of distribution of 0.3 (10) when calculating bicarbonate requirements although volumes of distributions of 0.5 have been advocated for calves (11). The apparent volume of distribution of bicarbonate was 0.73 and 0.78 L/kg in experiments 1 and 2. Calculations from experiments with acidotic scouring calves (1) indicate that the volume of distribution of bicarbonate is 0.65. The large volume of distribution in calves can be explained by the large extracellular fluid volume of the neonatal calf- 0.56 L/kg (12). Taken together this information confirms that values of 0.5, or more, should be used when calculating bicarbonate requirements for calves.

When a base is infused into a calf, the blood concentration rises and

stimulates utilization. If the base is efficiently metabolized, the rise in blood concentration will be small. If the base is not metabolized it accumulates in blood until renal excretion matches the rate of infusion. Acetate had the lowest blood concentrations indicating that metabolism of this base is efficient.

D-gluconate was not metabolized by the calf, there was no alkalinizing effect and blood gluconate concentrations rose to high values as the gluconate accumulated in blood. Although gluconate is used in some intravenous solutions, controlled studies of its alkalinizing effects are difficult to find (2). A study in dogs indicated that a multiple electrolyte solution containing gluconate and acetate had an alkalinizing effect. This was much less than that seen with bicarbonate and may have been solely due to the acetate component (13).

Racemic mixtures of DL-lactate are routinely used to make lactated Ringer's solution. Hartmann's original studies showed that DL-lactate was a good alkalinizing agent (14). Later work suggested that D-lactate might not be metabolized because more lactate was excreted in the urine when DL-lactate was infused than when L-lactate was used (15). Our studies confirm that L-lactate is much better metabolized than DL-lactate. Blood concentrations of D-lactate were much higher than for L-lactate which suggests that D-lactate metabolism is slow. Over 50% of the infused lactate was the D isomer but the racemic mixture had an alkalinizing effect that was over half of that for L-lactate. This indicates some of the D-lactate may have been metabolized, a view which is supported by studies in rats (16).

In experiment 1 there were marked changes in blood pH but changes in the partial pressure of carbon dioxide between infusions did not attain statistical significance. This suggests that respiratory compensation for alkalosis is poor or slow in neonatal calves.

Experiment 3 provided clear evidence for the superiority of acetate over L-lactate. In experiment 1 acetate was not statistically superior to L-lactate although the magnitude of the alkalinizing response was similar in

experiments 1 and 3. Statistically significant trends were more easily detectable in experiment 3 because the two bases were compared directly and the relatively less sensitive method of Tukey's means comparison was not needed. Sensitivity was also increased in experiment 3 because analyses were performed on the changes in base excess from the zero hour value, this removes initial baseline variation from the data. The lower blood concentrations of acetate than L-lactate are also consistent with more efficient acetate metabolism. A possible biochemical basis for this superiority is that less oxygen is required for acetate than L-lactate oxidation.

As a group L-lactate and acetate had a greater alkalinizing effect in calves between six and ten days of age than in two to five day old calves (Figs. 7 and 8). This is presumably due to a maturation of enzyme systems as calves age. Diarrheic calves under a week of age tend to have a lactic acidosis whereas calves older than a week tend to have a nonlactic acidosis (17). The improvement in metabolism seen in calves over a week of age in the present study is not sufficient to account for this difference. The improvement is small and changes in blood lactate concentrations during lactate loading were similar in both age groups (Fig. 9).

In experiments 4 and 5 citrate infusions were associated with the development of neuromuscular disturbances characterized by tetany followed by collapse and weakness. These signs are reminiscent of hypocalcemia. Total plasma calcium concentrations rose during citrate infusions. *In vitro* studies indicated that these calcium values are reliable because citric acid did not affect the assay of serum calcium. Ionized calcium is responsible for biological activity and it is possible that the signs of tetany and weakness seen during citrate infusion are due to a reduction in ionized calcium availability. Alternatively citrate may be binding to other ions, such as magnesium, and this may have contributed to the signs. Experiments in which ionized calcium and magnesium are measured are needed to sort out these possibilities.

In conclusion we have shown that acetate, L-lactate and propionate have

alkalinizing ability equivalent to bicarbonate in healthy calves. This does not imply that these bases would be equally effective in sick calves where metabolism may be impaired. In fact we have shown that bicarbonate is superior to L-lactate and acetate in correcting acidosis in diarrheic calves (1). Interestingly this study of diarrheic calves also indicated that acetate was marginally better than L-lactate. This is consistent with the results of the present study. D-lactate, gluconate and citrate are unsuitable for use as intravenous alkalinizing agents, the first two are ineffective and the latter leads to neuromuscular disturbances.

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